The rate of correction should be comparatively slow in *chronic* hyponatremia (<8–10 m*M* in the first 24 h and <18 m*M* in the first 48 h), so as to avoid ODS; lower target rates are appropriate in patients at particular risk for ODS, such as alcoholics or hypokalemic patients. Overcorrection of the plasma Na^+ concentration can occur when AVP levels rapidly normalize, for example following the treatment of patients with chronic hypovolemic hyponatremia with intravenous saline or following glucocorticoid replacement of patients with hypopituitarism and secondary adrenal failure. Approximately 10% of patients treated with vaptans will overcorrect; the risk is increased if water intake is not liberalized. In the event that the plasma Na^+ concentration overcorrects following therapy, be it with hypertonic saline, isotonic saline, or a vaptan, hyponatremia can be safely reinduced or stabilized by the administration of the AVP *agonist* desmopressin acetate (DDAVP) and/or the administration of free water, typically intravenous D_5W; the goal is to prevent or reverse the development of ODS. Alternatively, the treatment of patients with marked hyponatremia can be initiated with the twice-daily administration of DDAVP to maintain constant AVP bioactivity, combined with the administration of hypertonic saline to slowly correct the serum sodium in a more controlled fashion, thus reducing upfront the risk of overcorrection.

HYPERNATREMIA

Etiology Hypernatremia is defined as an increase in the plasma Na^+ concentration to >145 m*M*. Considerably less common than hyponatremia, hypernatremia is nonetheless associated with mortality rates of as high as 40–60%, mostly due to the severity of the associated underlying disease processes. Hypernatremia is usually the result of a combined water and electrolyte deficit, with losses of H_2O in excess of Na^+. Less frequently, the ingestion or iatrogenic administration of excess Na^+ can be causative, for example after IV administration of excessive hypertonic Na^+-Cl^- or Na^+-HCO_3^- (Fig. 63-6).

Elderly individuals with reduced thirst and/or diminished access to fluids are at the highest risk of developing hypernatremia. Patients with hypernatremia may rarely have a central defect in hypothalamic osmoreceptor function, with a mixture of both decreased thirst and reduced AVP secretion. Causes of this adipsic diabetes insipidus include primary or metastatic tumor, occlusion or ligation of the anterior communicating artery, trauma, hydrocephalus, and inflammation.

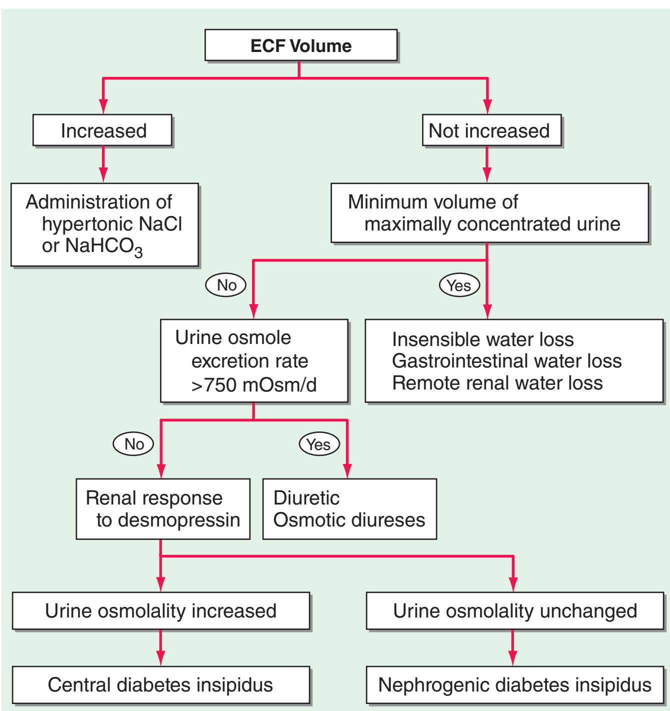

FIGURE 63-6 The diagnostic approach to hypernatremia. ECF, extracellular fluid.

Hypernatremia can develop following the loss of water via both renal and nonrenal routes. Insensible losses of water may increase in the setting of fever, exercise, heat exposure, severe burns, or mechanical ventilation. Diarrhea is, in turn, the most common gastrointestinal cause of hypernatremia. Notably, osmotic diarrhea and viral gastroenteritides typically generate stools with Na^+ and K^+ <100 m*M*, thus leading to water loss and hypernatremia; in contrast, secretory diarrhea typically results in isotonic stool and thus hypovolemia with or without hypovolemic hyponatremia.

Common causes of renal water loss include osmotic diuresis secondary to hyperglycemia, excess urea, postobstructive diuresis, or mannitol; these disorders share an increase in urinary solute excretion and urinary osmolality (see "Diagnostic Approach," below). Hypernatremia due to a water diuresis occurs in central or nephrogenic diabetes insipidus (DI).

Nephrogenic DI (NDI) is characterized by renal resistance to AVP, which can be partial or complete (see "Diagnostic Approach," below). Genetic causes include loss-of-function mutations in the X-linked V_2 receptor; mutations in the AVP-responsive aquaporin-2 water channel can cause autosomal recessive and autosomal dominant NDI, whereas recessive deficiency of the aquaporin-1 water channel causes a more modest concentrating defect (Fig. 63-2). Hypercalcemia can also cause polyuria and NDI; calcium signals directly through the calcium-sensing receptor to downregulate Na^+, K^+, and Cl^- transport by the TALH and water transport in principal cells, thus reducing renal concentrating ability in hypercalcemia. Another common acquired cause of NDI is hypokalemia, which inhibits the renal response to AVP and downregulates aquaporin-2 expression. Several drugs can cause acquired NDI, in particular lithium, ifosfamide, and several antiviral agents. Lithium causes NDI by multiple mechanisms, including direct inhibition of renal glycogen synthase kinase-3 (GSK3), a kinase thought to be the pharmacologic target of lithium in bipolar disease; GSK3 is required for the response of principal cells to AVP. The entry of lithium through the amiloride-sensitive Na^+ channel ENaC (Fig. 63-4) is required for the effect of the drug on principal cells, such that combined therapy within lithium and amiloride can mitigate lithium-associated NDI. However, lithium causes chronic tubulointerstitial scarring and chronic kidney disease after prolonged therapy, such that patients may have a persistent NDI long after stopping the drug, with a reduced therapeutic benefit from amiloride.

Finally, gestational DI is a rare complication of late-term pregnancy wherein increased activity of a circulating placental protease with "vasopressinase" activity leads to reduced circulating AVP and polyuria, often accompanied by hypernatremia. DDAVP is an effective therapy for this syndrome, given its resistance to the vasopressinase enzyme.

Clinical Features Hypernatremia increases osmolality of the ECF, generating an osmotic gradient between the ECF and ICF, an efflux of intracellular water, and cellular shrinkage. As in hyponatremia, the symptoms of hypernatremia are predominantly neurologic. Altered mental status is the most frequent manifestation, ranging from mild confusion and lethargy to deep coma. The sudden shrinkage of brain cells in acute hypernatremia may lead to parenchymal or subarachnoid hemorrhages and/or subdural hematomas; however, these vascular complications are primarily encountered in pediatric and neonatal patients. Osmotic damage to muscle membranes can also lead to hypernatremic rhabdomyolysis. Brain cells accommodate to a chronic increase in ECF osmolality (>48 h) by activating membrane transporters that mediate influx and intracellular accumulation of organic osmolytes (creatine, betaine, glutamate, myoinositol, and taurine); this results in an increase in ICF water and normalization of brain parenchymal volume. In consequence, patients with *chronic* hypernatremia are less likely to develop severe neurologic compromise. However, the cellular response to chronic hypernatremia predisposes these patients to the development of cerebral edema and seizures during overly rapid hydration (overcorrection of plasma Na^+ concentration by >10 m*M*/d).

Diagnostic Approach The history should focus on the presence or absence of thirst, polyuria, and/or an extrarenal source for water loss,